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How lipids contribute to ion channel function, a fat perspective on direct and indirect interactions

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Membrane lipid composition and remodeling influence the function of ion channels. Polyunsaturated fatty acids (PUFAs) and their derivatives modulate ion channel function; whether this effect occurs directly by binding to the protein or indirectly through alteration of membranes' mechanical properties has been difficult to distinguish. There are a large number of studies addressing the effect of fatty acids; recent structural and functional analyses have identified binding sites and provided further evidence for the role of the plasma membrane in ion channel function. Here, we review cation channels that do not share a common topology or lipid-binding signature sequence, but for which there are recent compelling data that support both direct and indirect modulation by PUFAs or their derivatives.

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Introduction

Biological membranes are very heterogeneous, not only in composition but also in spatial and temporal distribution [1••]. They carry out multiple physiological roles, including acting as a physical barrier for ions and solutes, regulating membrane protein function, and mediating signal transmission. Singer and Nicolson proposed the fluid mosaic model 45 years ago to describe the structure of cell membranes [2]. Even though our view of biological membranes has not stood still since 1972, the model has aged considerably well. New fundamental concepts have been established to further understand the dynamic relationships between membranes and the proteins embedded in them [3]. For instance, the arrangement between membrane proteins and the lipid bilayer allows communication in two directions: one in which the lipid composition influences protein function and the other in which proteins perturb the surrounding bilayer while undergoing conformational changes [4]. Polyunsaturated fatty acids (PUFAs) are among the membrane lipid components that dynamically regulate membrane protein function. PUFAs are essential molecules that regulate gene expression, receptor signaling, and plasma membrane remodeling [5]. Notably, membranes containing different levels of PUFAs feature distinct elastic properties [6,7]. PUFAs occur esterified or as free fatty acids cleaved from the plasma membrane by phospholipases (PL: A_1, A_2, C, and D). Once released, PUFAs can be further metabolized [8], act as second messengers [9], interact with membrane proteins [10•], and/or alter the mechanical properties of the bilayer [11••,12••,13,14,15••]. Yet distinguishing between some of these modalities has been quite challenging.

The 'force-from-lipids' principle [16•] establishes that changes in bilayer force provide the energy that is needed to drive or facilitate conformational rearrangements underlying ion channel opening and closing (*i.e.* gating).

This principle was first demonstrated 30 years ago when the purified bacterial mechanosensitive channel of large conductance (MscL) remained mechanosensitive even after reconstitution into pure bilayers [17]. However, the force-from-lipids effect also applies to other families of ion channels. Importantly, recent structure–function studies have demonstrated that lipids could also contribute to channel gating via direct lipid–protein interaction. As the direct effect of PUFAs on voltage-gated Na^+, K^+, and Ca^{2+} channels has been reviewed elsewhere [10•], we will focus on other cation channels (Table 1) that do not necessarily share a common topology or PUFA-binding signature sequence, such as: glutamate receptors (N-methyl-D-aspartate receptor, NMDA), transient receptor potential (TRP) channels, mechanotransduction channel complexes, pentameric ligand-gated ion channels (pLGICs), and Ca^{2+}-activated large-conductance K^+ (BK) channels.

Ion channels whose function are influenced by the mechanical properties of the membrane

NMDA receptors and membrane tension

NMDA receptors are glutamate-gated ion channels crucial for neuronal communication, synaptic plasticity, and cognitive functions [18]. Nearly 25 years ago, it was shown in cultured neurons that NMDA receptor currents are potentiated by arachidonic acid (AA) [19],

Table 1

Ion channels modulated directly and/or indirectly by lipids

Type of interaction	Ion channel	Lipid	Effect on function	Reference
Indirect	NMDA	AA	Potentiation	[23•]
	TRP and TRPL	PIP_2 depletion	Activation	[12••,25]
	C. elegans mechanoreceptor complex	AA-containing phospholipids	Enhance activation	[14]
	TRPV4	EEQ-containing phospholipids	Enhance activation	[15••]
Direct	pLGIC	DHA	Enhance desensitization	[34••,35]
	BK	DHA	Activation	[38,39••,40••]
	BK	LTB4	Enhance activation	[41•]
	TRPV1	LPA	Activation	[48••,49]
	TRPV1	Anandamide	Activation	[50,52••,54•]

docosahexaenoic acid (DHA) [20], and osmotic pressure [21], but inhibited by lysophospholipids (LPLs) [22]. Interestingly, mutagenesis studies ruled out the direct interaction between AA or LPL and the putative NMDA receptor fatty acid binding domain [22]. Still, after dismissing a direct interaction between fat molecules and the channel, it was unknown whether the receptors' gating properties responded to changes in membrane tension due to the incorporation of fatty acids and LPL. Following a reductionist approach of reconstituting purified channels into liposomes, Kloda and colleagues demonstrated that NMDA receptor function is enhanced by increasing the membrane lateral tension with negative pressure or AA incorporation [23•]. Thanks to the ensemble of *ex vivo* and *in vitro* experiments, it is now recognized that AA modulates NMDA receptor gating by changes in bilayer mechanical properties rather than by specific protein-binding events.

Light-sensitive TRP and TRP-like channels and phospholipid hydrolysis

Phototransduction in *Drosophila melanogaster* is mediated by phospholipase C (PLC) and the subsequent activation of two distinct ion channels, TRP and TRP-like (L) [24]. For many years, the leading hypothesis was that PLC-mediated hydrolysis of PIP_2 yielded the second messengers diacylglycerol and IP_3, and a proton that gated these channels [16•]. This natural assumption was challenged by the remarkable finding from Hardie and Franze [12••,25] in which PIP_2 depletion evokes changes in the mechanical properties of the membrane that in turn activates TRP and TRPL channels [24] (Figure 1a). Furthermore, increasing lipid crowding with cationic amphiphiles inhibited the photoreceptor light responses, suggesting the membrane as a key modulator of channel gating. These results were also supported by experiments in which manipulating the fly's diet (*e.g.* food without PUFAs) to increase plasma membrane stiffness slowed down light-induced responses [26]. The current model highlights the contribution of the membrane by supporting the idea that reduction in area, volume, and phospholipid crowding following PIP_2 hydrolysis ultimately favors the protonation of previously buried sites in TRP and TRPL channels, which in turn promote channel gating [24].

Caenorhabditis elegans mechanoreceptor complex and AA-containing phospholipids

Mechanoelectrical transduction in *C. elegans* touch receptor neurons (TRNs) relies on at least 12 MEC proteins (MEC stands for proteins that when mutated confer mechanosensory abnormal phenotypes), including ion channels from the DEG/ENaC/ASIC family (MEC-4 and MEC-10) [27]. Recently, AA-containing phospholipids were shown to enhance the function of this multiprotein complex in the mechanical response of TRNs *in vivo* [14]. By examining the touch-elicited behavior of worms genetically unable to generate PUFAs, Vásquez *et al.* established that AA exerts its effect on mechanoelectrical transduction by influencing the viscoelastic properties of the plasma membrane rather than acting as a signaling molecule [14]. This was demonstrated by pulling membrane nanotubes with an atomic force microscopy (AFM) cantilever from the plasma membrane of native TRNs or TRNs genetically depleted of long PUFAs. In this context, one could imagine that the response of neurons to mechanical stimuli might be modulated by the presence of polyunsaturated bonds in the lipid acyl chains, creating a distinctive membrane environment that enhances the function of mechanoelectrical transduction channel complexes.

TRP vanilloid 4 and fatty acids

The TRP vanilloid 4 (TRPV4) channel contributes to intracellular Ca^{2+} homeostasis and is essential in mediating various physiological (*e.g.* vascular tone) and pathological conditions (*e.g.* neuromuscular diseases) [28]. TRPV4 is a polymodal ion channel activated by thermal, osmotic, and chemical stimuli [28]. Furthermore, ω-6 PUFAs, such as AA and its epoxyeicosatrienoic acid metabolites, have been shown to activate TRPV4 downstream of cell swelling [29,30]. Alternatively, it has been recently demonstrated that TRPV4 function greatly relies on the membrane environment. Plasma membranes